δ 1.36 (3 H, t), 2.23 (3 H, s), 2.44 (3 H, d, J = 2.6 Hz), 4.35 (2 H, q); ^{19}F NMR δ −122.8 (d, J = 2.5 Hz); ^{13}C NMR δ 13.83 (CH_3), 20.36 (CH_3), 25.00 (CH_3), 64.40 (CH_2O), 102.14 (d, $J_{C,F}$ = 251.8 Hz, CF), 163.19 (d, $J_{C,F}$ = 30.2, COO), 168.86 (s, COO), 197.68 (d, $J_{C,F}$ = 30.7 Hz, CO). **3-Chloro-3-fluoro-2,4-pentanedione (5c)** was prepared starting from **4c**; reaction time 2 h; eluting system for flash chromatography n-hexane/CH_2Cl_2, 85:15; yield 95%, ^{1}H NMR δ 2.48 (d, J = 2.7 Hz); ^{19}F NMR δ −126.2 (septet, J = 2.7 Hz); ^{13}C NMR δ 24.95 (CH_3), 102.84 (d, $J_{C,F}$ = 269.6 Hz, CF), 197.48 (d, $J_{C,F}$ = 27.0 Hz, CO); IR (film) 2925, 1738 (CO) cm^{-1}; MS (CI) m/e 153 and 155 (M^+ + 1). **1,3-Dimethyl-5,5-difluorobarbituric acid (5e)** was prepared starting from 1,3-dimethylbarbituric acid (**4e**) and 2.2 equiv of 1; acetonitrile was used as reaction solvent; reaction time 6 h; eluting system for flash chromatography n-hexane/ethyl acetate 7:3; yield 95%; mp 125–127 °C; ^{1}H NMR δ 3.40 (s); ^{1}H NMR (CD_3CN) δ 3.26 (t, J = 0.5 Hz); ^{19}F NMR δ −108.7; ^{13}C NMR (CD_3CN) δ 29.64 (CH_3), 99.61 (t, $J_{C,F}$ = 245.5 Hz, CF_2), 150.35 (NCON), 160.97 (t, $J_{C,F}$ = 27.8 Hz, $COCF_2$); IR (Nujol) 1687 (CO), 1448, 1304 cm^{-1}; MS (EI) m/e 192 (M^+), 176, 135, 107, 78.

Ethyl 3-fluoro-3-methyl-2-oxobutanoate (7a) was prepared starting from **6a**; reaction time 27 h; eluting system for flash chromatography n-hexane/ethyl ether, 6:4; yield 95%; ^{1}H NMR δ 1.39 (3 H, t), 1.64 (6 H, d, J = 21.6 Hz), 4.41 (2 H, q); ^{19}F NMR δ −151.4 (septet, J = 21.3 Hz) (^{19}F NMR δ −152.0 (septet, J = 21.3 Hz, ref 13)); ^{13}C NMR δ 13.87 (CH_3), 24.14 (d, $J_{C,F}$ = 24.1 Hz, CH_3), 64.00 (CH_2O), 97.85 (d, $J_{C,F}$ = 177.9 Hz, CF), 164.08 (COO), 196.82 (d, $J_{C,F}$ = 35.3 Hz, CO), MS (CI) m/e 163 (M^+ + 1), 143. **3-Fluoro-3-methyl-2-oxopentanoic acid (7b)** was prepared starting from **6b**; $CHCl_3$ saturated with H_2SO_4 was used as reaction solvent; reaction time 24 h; eluting system for flash chromatography CH_2Cl_2/ethyl acetate/acetic acid, 50:50:0.5; yield 95%; ^{1}H NMR δ 0.98 (3 H, d, J = 21.8 Hz), 1.9–2.2 (2 H, m); ^{19}F NMR δ −160.1 (sextet, J = 21.5 Hz); ^{13}C NMR δ 7.05 (CH_3), 21.86 (d, $J_{C,F}$ = 23.2 Hz, CH_3), 30.39 (d, $J_{C,F}$ = 22.5 Hz, CH_2), 99.95 (d, $J_{C,F}$ = 182.0 Hz, CF), 163.5 (COOH), 195.5 (d, $J_{C,F}$ = 32.9 Hz, CO); IR (film) 3300–2500 (COOH), 1748, 1193 cm^{-1}; MS (EI) m/e 148 (M^+), 128, 121, 75. **3-Fluoro-2-oxobutanoic acid (7c)** was prepared starting from **6c**; reaction time 18 h; eluting system for flash chromatography CH_2Cl_2/ethyl acetate/acetic acid, 50:50:0.5; yield 95%; ^{1}H NMR (D_2O) δ 1.36 (3 H, dd, J = 6.3, 25.5 Hz, CH_3), 4.86 (1 H, dq, J = 6.3, 46.7 Hz, CHF); ^{19}F NMR (D_2O) δ −186.2 (dq, J = 25.6, 47.6 Hz); ^{13}C NMR (D_2O) δ 12.74 (d, $J_{C,F}$ = 21.6 Hz, CH_3), 90.97 (d, $J_{C,F}$ = 172.7 Hz, CF), 92.90 (d, $J_{C,F}$ = 23.4 Hz, OCO of the hydrated ketone), 171.92 (COOH).

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Supplementary Material Available: ^{1}H NMR spectra of all new compounds (15 pages). Ordering information is given on any current masthead page.

Synthesis of Synvinolin: Extremely High Conversion Alkylation of an Ester Enolate

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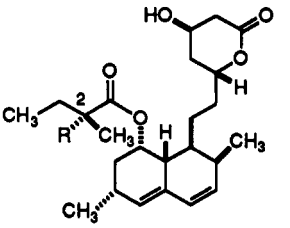
A efficient process for the commercial preparation of the therapeutically important cholesterol lowering drug synvinolin (2: simvastatin, ZOCOR) from mevinolin (1: lovastatin, MEVACOR) is reported. The synthesis relies upon deactivation of the δ-lactone carbonyl toward enolization via conversion to the bis[(*tert*-butyldimethylsilyl)oxy] butylamide 7. An extremely high conversion (99.7%) ester enolate alkylation of 7 affords 8 and 9. Subsequent desilylation and intramolecularly assisted basic amide hydrolysis in the presence of the dimethylbutyrate ester moiety yields 12, which is lactonized to 2. The overall yield from 1 to 2 is 86%.

Introduction

The naturally occurring fungal metabolite mevinolin (1: lovastatin, MEVACOR)[1,2] and the more active semisynthetic derivative[3] synvinolin (2: simvastatin, ZOCOR)[3b] are pharmacologically useful compounds for the lowering of serum cholesterol levels.[4] Although several methods



1 R = H Mevinolin (Lovastatin, MEVACOR®)

2 R = CH_3 Synvinolin (Simvastatin, ZOCOR®)

are available for conversion of 1 to 2, all are complicated by the inability to remove even trace amounts of 1 from

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(2) Mevinolin total synthesis: (a) Hirama, M.; Iwashita, M. *Tetrahedron Lett.* **1983**, *24*, 1811. (b) Clive, D. L. J.; Keshava Murthy, K. S.; Wee, A. G. H.; Prasad, J. S.; daSilva, G. V. J.; Majewski, M.; Anderson, P. C.; Haugen, R. D.; Heerze, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 6914. (c) Wovkulich, P. M.; Tang, P. C.; Chadha, N. K.; Batchco, A. D.; Barrish, J. C.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1989**, *111*, 2596. (d) For a review on the synthesis of Mevinic acids, see: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909.

(3) Mevinolin semisynthetic derivatives: (a) Kuo, C. H.; Patchett, A. A.; Wendler, N. L. *J. Org. Chem.* **1983**, *48*, 1991. (b) Hoffman, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 849. (c) Stokker, G. E.; Rooney, C. S.; Wiggins, J. M.; Hirshfield, J. *J. Org. Chem.* **1986**, *51*, 4931. (d) DeCamp, A. E.; Verhoeven, T. R.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3207.

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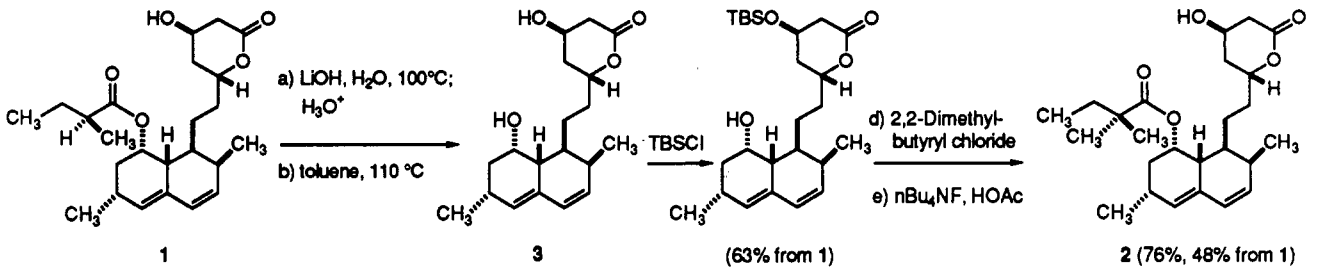
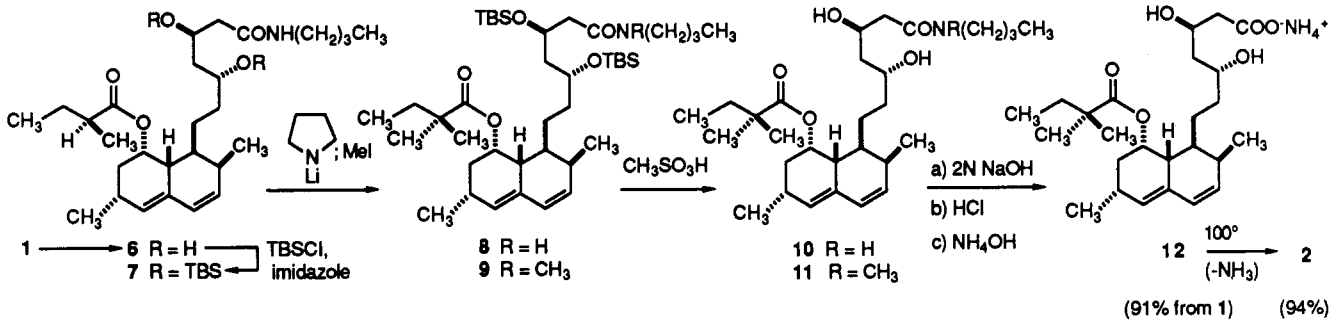
0022-3263/91/1956-4929$02.50/0

Scheme I



Scheme II

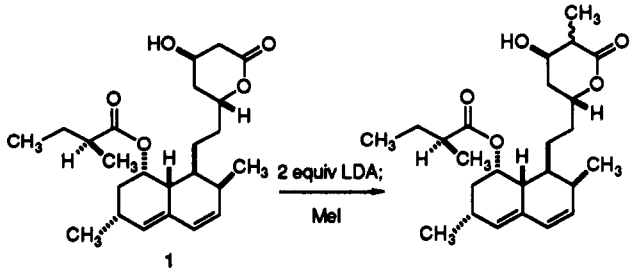


2 by fractional crystallization.[5] Thus, any practical large-scale process for preparing 2 must effectively reduce residual amounts of 1 to very low levels (<0.5%). Compound 2 has been prepared from 1 via a straightforward five-step process of (1) exhaustive saponification; (2) relactonization to afford 3; (3) selective silylation; (4) reacylation; and (5) desilylation (Scheme I). However, the overall yield from 1 to 2 by this method is only 48%, due in part to the very hindered nature of the axial 2(*S*)-methylbutyrate side chain.[6]

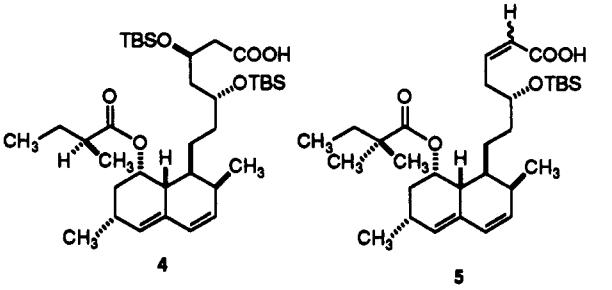
In this paper, we report chemistry that forms the foundation for a commercially important process for the preparation of 2 from 1. This chemistry is highlighted by an extremely high conversion ester enolate alkylation and an unusual basic amide hydrolysis in the presence of an ester function.

Results and Discussion

To circumvent the problematic deacylation/reacylation sequence, approaches involving enolization/methylation of the 2(*S*)-methylbutyrate side chain were examined. Deactivation of the δ-lactone carbonyl was necessary for the success of this approach, since the lactone moiety was more reactive, due to its greater acidity[7] (eq 1). Preliminary results were obtained on the protected carboxylic acid 4[8] with lithium pyrrolidide as the base for enolization.[9] Inspection of the crude ^{1}H NMR spectrum after methylation with excess methyl iodide revealed the presence of new olefinic resonances attributed to the unsaturated acids 5. This implied that further deprotonation of the intermediate lithium carboxylate–ester enolate was occurring, resulting in elimination of the silyloxy group. Interestingly, it has been reported that the effective pK_a of lithium carboxylates in THF is only a few units higher than that of the corresponding esters.[10]



eq 1



Attention was next turned to the protected butyl amide derivative 7 as a more desirable intermediate in the methylation step (Scheme II). It was speculated that the lithium imidate form of 7 would be less prone toward elimination of the silyloxy group with excess base than the corresponding lithium carboxylate derived from 4 due to the high second pK_a of the lithium imidate. It was hoped that hydrolysis of the amide moiety after methylation would be faster than saponification of the hindered ester side chain, due to the possibility of intramolecular hydroxyl group participation during hydrolysis.

Treatment of 1 with butylamine at the reflux point (80 °C) followed by removal of the excess butylamine at re-

(5) Melting points (dec): mevinolin (1) mp 174.5 °C; synvinolin (2) mp 139.5 °C. Repeated recrystallization of mixtures of 1 and 2 results in enrichment of 1 irrespective of the relative amounts in the starting mixture.

(6) Willard, A. K.; Smith, R. L. *J. Labelled Compd. Radiopharm.* **1982**, *19*, 337.

(7) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1988**, *110*, 1872.

(8) Acid 4 was prepared from 1 via saponification with 5 N KOH in THF (1.0 equiv, 0 °C) followed by azeotropic distillation to remove water and treatment with excess TBSCl/imidazole in DMF followed by quenching with aqueous methanol to effect silyl ester cleavage.

(9) After a brief screening of bases for the enolization/methylation step, it was determined that lithium pyrrolidide gave higher conversions than LDA or lithium hexamethyldisilazide. This is most likely due to the steric requirements for deprotonation of the hindered 2(*S*)-methylbutyrate ester.

(10) Gronert, S.; Streitweiser, A. *J. Am. Chem. Soc.* **1988**, *110*, 4418.

Table I. Effect of Methyl Iodide Charge and Age Temperature on Conversion and N-Methylation in Methylations of 7[a]

entry	final age temp (°C)	equiv of MeI	ratio 8:9[b]	% convn[b]
1	-10	3.0	3	99.7
2	-10	2.0	4	99.7
3	-10	1.5	12	99.7
4	-30	1.5	30	99.5

[a] All alkylations run at 0.10 M in amide in THF/cyclohexane (4:1, K.F. < 100 mg/L) with 2.3 equiv of lithium pyrrolidide (-35 °C, 2 h) followed by MeI addition and aging (-30 °C, 1 h; warm to final age temperature, 20 min, then aqueous quench). [b] % Conversion = [peak area (8 + 9)/peak area (7 + 2-epi-7[12] + 8 + 9)] × 100 as determined by HPLC analysis of the crude methylation reaction.

Table II. Effect of Water and Base Charge on Conversion in Methylations of 7[a]

entry	$[H_2O]$, mg/L	base equiv	MeI equiv	% convn
1	87	2.3	1.5	99.7
2	199	2.3	1.5	96.5
3	390	2.3	1.5	78.9
4	352	3.0	2.2	99.8
5	<100	3.0	1.1	83.6[b]

[a] All alkylations run at 0.10 M in amide in 4:1 THF/cyclohexane. Enolization was carried out at -35 °C (2 h) followed by MeI addition and aging (-30 °C, 1 h; -10 °C, 20 min). [b] Gives 99.8% conversion upon addition of 1.1 equiv of MeI.

duced pressure and silylation of the resulting diol 6 affords the protected amide 7 in one pot (99%). Enolization of crude 7 with 2.3 equiv of lithium pyrrolidide followed by quenching with methyl iodide gives extremely high conversion methylations[11] (99.5–99.7%) to afford 8 (Table I). Depending on the excess of methyl iodide present and the temperature at final aqueous quenching, varying amounts of N-methylated amide 9 are also obtained. It was noted that use of 1.5 equiv of methyl iodide and a final age temperature of -10 °C gave an extremely high conversion alkylation (99.7% reproducibly) while suppressing the formation of large amounts of *N*-methylamide 9 (entry 3), which is advantageous in the hydrolysis step (vide infra). Thus *with a single charge of 2.3 equiv of lithium pyrrolidide, essentially quantitative enolization of the hindered methylbutyrate side chain is effected at -35 °C.* HPLC analysis after the methylation step reveals only small amounts (1–2%) of products derived from elimination of silanol.

The effects of water and base charge have been studied on the conversion in the methylation reaction (Table II). It is apparent from the data that the amount of water tolerable in the mixture is greater with a larger excess of lithium pyrrolidide, as expected. It should also be noted that some of the methyl iodide is consumed by lithium pyrrolidide as indicated by a large excess of base (entry 5); however, additional excess methyl iodide gives complete conversion.

Deblocking of the silyl ether intermediates 8 and 9 occurs in one pot. Acid-catalyzed silyl transfer with methanesulfonic acid in aqueous methanol affords the dihydroxy amides 10 and 11. Direct hydroxide addition to the desilylation reaction followed by heating results in complete amide hydrolysis to the hydroxy carboxylate form of lactone 2. By HPLC analysis, hydrolysis of the tertiary amide 11 was approximately twice as slow as the secondary amide 10. Remarkably, little if any saponification of the ester side chain occurs during the relatively mild amide hydrolysis. HPLC analysis of the hydrolysis reaction at completion shows levels of 3[6] (Scheme I, hydroxy acid form) that are typically <2.0%.[13]

The product hydroxy acid is efficiently isolated as the highly crystalline ammonium salt derivative 12. The overall yield from mevinolin (1) to the crystalline synvinolin derivative 12 is 91%. Lactonization then affords synvinolin (2) in 94% yield.

Experimental Section

General. HPLC analyses were performed with a Spectra-Physics SP8700 solvent delivery system employing a Perkin-Elmer C18 3-cm reversed phase column, 3 μm particle size with detection at 238 nm in acetonitrile/THF/water buffered with 0.1 M NH_4OAc at 25 °C. Unless otherwise noted, all manipulations were carried out under an inert atmosphere of N_2 gas. In general, glassware was not specially dried prior to use. The following solvents and reagents were dried over 3A sieves prior to use: THF, butylamine, pyrrolidine, DMF; others were used as received. Karl Fisher titrations were run on a Brinkman 652 KF coulometer.

***N*-Butyl-7-[1,2,6,7,8,8a(*R*)-hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutanoyl]oxy]-1(*S*)-naphthyl]-3(*R*),5(*R*)-dihydroxyheptanoic Acid Amide (6).** 1 (50.30 g, 0.124 mol) and *n*-butylamine (42 mL, 0.42 mol, K.F. <0.1 g/L) are combined at 25 °C and heated to 80 °C for 1 h. The viscous solution was then cooled to 25 °C, and the excess butylamine was removed at reduced pressure to afford the crude amide 6 as a thick gum, 59.4 g (100%): ^1H NMR ($CDCl_3$, 300 MHz, selected data) δ 6.16 (bt, *J* = 5.4 Hz, 1 H), 5.98 (d, *J* = 9.6 Hz, 1 H), 5.77 (dd, *J* = 6.1, 9.6 Hz, 1 H), 5.50 (bt, *J* = 3.0 Hz, 1 H), 5.40 (bq, *J* = 2.9 Hz, 1 H), 4.79 (d, *J* = 1.9 Hz, 1 H), 4.19 (m, 1 H), 3.78 (m, 1 H), 3.69 (d, *J* = 2.3 Hz, 1 H), 3.24 (bq, *J* = 6.6 Hz, 2 H), 1.09 (d, *J* = 7.0 Hz, 3 H), 1.07 (d, *J* = 7.7 Hz, 3 H), 0.92 (t, *J* = 7.3 Hz, 3 H), 0.867 (t, *J* = 7.4 Hz, 3 H), 0.866 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 176.9, 171.8, 133.2, 131.6, 129.4, 128.1, 72.3, 69.5, 67.9, 42.9, 42.4, 41.4, 39.0, 37.4, 36.2, 34.8, 32.7, 31.5, 30.5, 27.4, 26.7, 24.1, 22.8, 20.0, 16.2, 13.8, 13.7, 11.6; IR ($CHCl_3$) λ_{max} 3600–3300 (b), 3450 (s), 1720, 1660, 1530, 1210, 730 cm^{-1}.

***N*-Butyl-7-[1,2,6,7,8,8a(*R*)-hexahydro-2(*S*),6(*R*)-dimethyl-8(*S*)-[[2(*S*)-methylbutanoyl]oxy]-1(*S*)-naphthyl]-3(*R*),5(*R*)-bis[(*tert*-butyldimethylsilyl)oxy]heptanoic Acid Amide (7).** The crude amide 6 from the previous step is dissolved in dimethylformamide (132 mL, K.F. <0.1 g/L) at 25 °C. Imidazole (19.59 g, 0.288 mol) and *tert*-butyldimethylsilyl chloride (44.4 g, 0.288 mol) are added, and the mixture is heated at 60 °C for 6 h. The mixture is then cooled to 12 °C, anhydrous methanol (5.8 mL, 0.143 mol) is added, and the mixture is aged at 10–15 °C for 30 min. The heterogeneous mixture is then partitioned with cyclohexane (1.5 L) and 5% aqueous $NaHCO_3$ (750 mL) and vigorously agitated. The layers are allowed to separate, and the cyclohexane phase is washed successively with 5% aqueous $NaHCO_3$ (750 mL) and distilled water (750 mL). The cyclohexane layer is then concentrated at ambient pressure to a volume of 580 mL. The concentrated solution is then diluted with sieve-dried THF (600 mL, K.F. 0.50 g/L), and then the pot volume is reduced to 870 mL while distilling at ambient pressure. HPLC assay at this point indicates 86.9 g (99%) of 7: ^1H NMR ($CDCl_3$, 300 MHz, selected data) δ 6.39 (bt, *J* = 5.2 Hz, 1 H), 5.96 (d, *J* = 9.7 Hz, 1 H), 5.77 (dd, *J* = 6.0, 9.7 Hz, 1 H), 5.49 (bs, 1 H), 5.30 (bq, *J* = 2.8 Hz, 1 H), 4.15 (m, 1 H), 3.57 (m, 1 H), 3.24 (m, 2 H), 1.08 (d, *J* = 7.0 Hz, 3 H), 1.05 (d, *J* = 7.4 Hz, 3 H), 0.91 (t, *J* = 7.3 Hz, 3 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 6 H), 0.04 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 176.2, 170.8, 133.3,

(11) % Conversion = [peak area (8 + 9)/peak area (7 + 2-epi-7[12] + 8 + 9)] × 100 as determined by HPLC analysis of the crude methylation reaction.

(12) The 2(*R*)-methylbutyrate epimer is formed by nonstereoselective protonation of the ester enolate during the methylation step.

(13) The 3-hydroxy acid present at the end of amide hydrolysis reaction (1–2%) is believed to arise from deacylation during the enolization prior to methylation, since essentially no further increase in its level (<0.1%) is observed by HPLC upon extended reflux (24 h) of the hydrolysis reaction after complete amide hydrolysis.

131.9, 129.5, 128.3, 70.3, 67.7, 67.2, 44.5, 43.4, 41.4, 39.0, 37.5, 36.5, 35.4, 32.7, 31.6, 30.8, 27.5, 26.8, 25.9 (3), 25.8 (3), 24.6, 22.8, 20.2, 18.0, 17.9, 16.0, 13.8, 13.75, 11.9, -4.0, -4.4, -4.6, -4.9; IR ($CHCl_3$) λ_{max} 3380, 1720, 1660, 1220, 840, 740 cm^{-1}.

N-Butyl-7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)-dimethyl-8(S)-[[2,2-dimethylbutanoyl]oxy]-1(S)-naphthyl]-3(R),5(R)-bis[(tert-butyldimethylsilyl)oxy]heptanoic Acid Amide (8). A solution of sieve-dried pyrrolidine (25.1 mL, 0.301 mol, K.F. <0.10 g/L) and THF (192 mL) is cooled to -18 °C. A solution of *n*-butyllithium in hexanes (1.60 M, 181 mL, 0.290 mol) is added at such a rate as to keep the temperature below -10 °C (approximately 15 min). After the addition is complete, the mixture is aged at -20 °C for 15 min. The solution of crude amide 7 in THF/cyclohexane is cooled to -35 °C. The -20 °C lithium pyrrolidide solution is added to the rapidly agitated solution of amide 7 at such a rate as to maintain the temperature below -30 °C at all times during addition. After the addition is complete, the mixture is aged at -30 to -35 °C for 2 h, and then methyl iodide (12.2 mL, 0.196 mol) is added in one portion. After an initial 20 °C exotherm, the solution is recooled to -30 °C, aged for 1 h, warmed to -10 °C, and aged for 20 min at -10 °C. Water (550 mL) is added, and the mixture is rapidly agitated for 10 min. The phases are separated, and the organic phase is washed with 10 °C 1 N HCl (550 mL). The resulting organic phase is concentrated at reduced pressure to 20% of the original volume, it contains the amide 8: ^1H NMR ($CDCl_3$, 300 MHz, selected data) δ 6.39 (bt, J = 5.4 Hz, 1 H), 5.96 (d, J = 9.7 Hz, 1 H), 5.76 (dd, J = 6.1, 9.7 Hz, 1 H), 5.47 (bt, J = 2.9 Hz, 1 H), 5.29 (bq, J = 2.9 Hz, 1 H), 4.17 (m, 1 H), 3.55 (m, 1 H), 3.25 (bm, 2 H), 1.15 (s, 3 H), 1.10 (s, 3 H), 1.05 (d, J = 7.4 Hz, 3 H), 0.91 (d, J = 7.2 Hz, 3 H), 0.88 (s, 9 H), 0.87 (s, 9 H), 0.84 (d, J = 7.0 Hz, 3 H), 0.82 (t, J = 7.5 Hz, 3 H), 0.08 (s, 3 H), 0.06 (s, 6 H), 0.05 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 177.4, 170.7, 133.0, 131.7, 129.5, 128.3, 70.4, 67.8, 67.1, 44.4, 43.2, 42.8, 39.0, 37.6, 36.4, 35.5, 32.8 (2), 31.6, 30.7, 27.2, 25.9 (3), 25.7 (3), 24.7, 24.6 (2), 23.0, 20.1, 17.9, 17.8, 13.7, 13.6, 9.3, -4.0, -4.4, -4.6, -5.0; IR ($CHCl_3$) λ_{max} 3370, 1720, 1660, 1260, 1210, 840, 735 cm^{-1}.

N-Butyl-7-[1,2,6,7,8,8a(R)-hexahydro-2(S),6(R)-dimethyl-8(S)-[[2,2-dimethylbutanoyl]oxy]-1(S)-naphthyl]-3(R),5(R)-dihydroxyheptanoic Acid Amide (10). Methanol (690 mL) is added to the concentrated crude solution of amide 8 followed by water (45.7 mL) and methanesulfonic acid (1.5 mL, 0.023 mol). The resulting solution is aged at 30 °C for 5 h. At the end of the age period desilylation is complete to the diol-amide 10: ^1H NMR ($CDCl_3$, 300 MHz, selected data) δ 6.14 (bt, J = 5.3 Hz, 1 H), 5.98 (d, J = 9.6 Hz, 1 H), 5.77 (dd, J = 6.1, 9.6 Hz, 1 H), 5.49 (bt, J = 2.9 Hz, 1 H), 5.41 (bq, J = 2.9 Hz, 1 H), 4.20 (m, 1 H), 3.78 (m, 1 H), 3.25 (bq, J = 6.8 Hz, 2 H), 1.12 (s, 3 H), 1.11 (s, 3 H), 1.09 (d, J = 7.4 Hz, 3 H), 0.92 (t, J = 7.2 Hz, 3 H), 0.86 (d, J = 7.1 Hz, 3 H), 0.82 (t, J = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 178.2, 171.8, 133.0, 131.5, 129.4, 128.2, 72.2, 69.5, 68.1, 43.0, 42.9, 42.4, 39.0, 37.7, 36.0, 34.7, 33.0, 32.9, 31.5, 30.4, 27.2, 24.7, 24.6, 24.1, 23.0, 20.0, 13.8, 13.6, 9.2; IR ($CHCl_3$) λ_{max} 3600-3300 (b), 3450 (s), 1710, 1660, 1220, 735 cm^{-1}.

6(R)-[2-[8(S)-[[2,2-Dimethylbutanoyl]oxy]-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (2). To the crude solution of amide 10 from the previous step is added 2 N NaOH (373 mL) at 25 °C, and the solution is heated while distillate is collected at ambient pressure. The distillation is continued until the vapor temperature is 72-73 °C and the pot temperature is 78-80 °C. At this point, collection of distillate is discontinued and the solution is aged at reflux for 2 h and then cooled to 40 °C. The pressure is reduced, and the solution is concentrated to remove most of the methanol. The heterogeneous mixture is then diluted with distilled water (228 mL) and cooled to 10 °C while adjusting the pH to 6-7 with 3 N HCl. Ethyl acetate (990 mL) is added, and the pH is further adjusted to 5.0 with 3 N HCl. After agitation, the phases are allowed to settle and are separated, and methanol (225 mL) is added to the ethyl acetate layer. Aqueous ammonium hydroxide/methanol (1:3, 75 mL) solution is added over a 1-h period; the mixture is then warmed to 45 °C, aged for 15 min, and cooled to -10 °C over 2.5 h. After aging at -10 °C for 1-2 h, the crystals of ammonium salt are filtered, washed with cold EtOAc/MeOH (3.5:1) solution, and dried overnight at 35 °C to afford 51.37 g (90.9% overall from mevinolin) of ammonium salt 12 at 98.9% weight purity by quantitative HPLC analysis. Recrystallization from acetonitrile yields an analytically pure sample. Anal. Calcd for $C_{25}H_{43}O_6N$: C, 66.20; H, 9.55; N, 3.09. Found: C, 66.16; H, 9.66; N, 2.88. The crude ammonium salt is suspended in toluene (1.03 L) and heated at 100 °C with a nitrogen sweep for 6 h. The solution is then cooled to 25 °C, and Darco KB (2.5 g) is added. The mixture is agitated at 25 °C for 30 min, filtered thru Celite, and concentrated to a thick oil at reduced pressure. Cyclohexane (140 mL) is added, and the solution again is concentrated. Cyclohexane (600 mL) is added, and the heterogeneous mixture is heated to reflux until all material has dissolved. The mixture is cooled to 10 °C, aged for 1 h, filtered, and washed with 250 mL of cold cyclohexane. The crystals are dried under vacuum at 30-35 °C to afford 44.6 g (94.2%) of 2. Recrystallization from methanol/water yields analytically pure material: ^1H NMR ($CDCl_3$, 250 MHz, selected data) δ 5.98 (d, J = 9.6 Hz, 1 H), 5.77 (dd, J = 6.0, 9.6 Hz, 1 H), 5.50 (bt, J = 3.0 Hz, 1 H), 5.35 (m, 1 H), 4.62 (m, 1 H), 4.36 (m, 1 H), 2.92 (m, 1 H), 2.77-2.57 (AB of an ABX, J = 17.6 Hz, 2 H), 1.12 (s, 3 H), 1.11 (s, 3 H), 1.08 (d, J = 7.4 Hz, 3 H), 0.88 (d, J = 7.0 Hz, 3 H), 0.82 (t, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 66.9 MHz) δ 177.9, 170.4, 132.8, 131.5, 129.6, 128.3, 76.4, 68.1, 62.5, 43.0, 38.6, 37.6, 36.6, 36.1, 33.0, 32.9, 30.6, 27.2, 24.7, 24.3, 23.0, 13.9, 9.3; IR ($CHCl_3$) λ_{max} 3600 (s), 3550-3350 (b), 2970, 1730-1715 (b), 1210, 1165 cm^{-1}. Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.97; H, 9.26.

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Supplementary Material Available: NMR spectra (^1H and/or ^{13}C/APT) for compounds 2, 4, 5-8, 10, and 12 plus HPLC traces for the enolization/methylation of 7, supporting the high conversion methylation (21 pages). Ordering information is given on any current masthead page.